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EXAMINER
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ART UNIT	PAPER NUMBER
1642	9

DATE MAILED: 09/25/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/745,506	Lal et al
Examiner	**Art Unit**
Karen Canella	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3 months* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____ .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *23-42* is/are pending in the application.

4a) Of the above, claim(s) *23, 24, 34-38, and 40* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *25-33, 39, 41, and 42* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *2,3*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Acknowledgment is made of applicant's election with traverse or Group II, drawn to polynucleotides comprising SEQ ID NO: 74, polynucleotides encoding SEQ ID NO:37, complementary sequences, microarrays, vectors, host cells and recombinant methods of expression thereof. The traversal is on the grounds that the restriction is improper as it separates the invention of Group I, drawn to polypeptides, as well as separating the inventions drawn to methods of using said polynucleotides products. Applicant argues that it would not be an additional burden to search the polypeptides of the invention along with the elected polynucleotides. Applicants cite *In re Ochiai* in support of re-joinder of the method claims at the time of allowability of said product claims. With regard to the method claims, the policies set forth in the Commissioner's Notice of February 28, 1996 published on March 26, 1996 at 1184 O.G. 86 will be followed. Method claims limited to the scope of the allowable product claims will be rejoined and examined at the time the product claims are indicated as being allowable. However, the rejoinder claims drawn to polypeptides has been considered but not found persuasive. Inventions I and II are structurally and functionally different products which are made by different methods and have different uses. As to the question of burden of search, the claims of Groups I and II are classified differently, necessitating different searches in the U.S. Patent shoes. Further, classification of subject matter is merely one indication of the burdensome nature of the search involved. The literature search, particularly relevant in this art, is not co-extensive and is much more important in evaluating the burden of search. Clearly different searches and issues are involved in the examination of each group.

Applicant has elected the polynucleotides encoding SEQ ID NO:37 and the polynucleotide of SEQ ID NO:74. Said sequences are part of Markush groups recited in claims 24, 27 and 32. Applicant argues that it is improper for a Markush group to be restricted apart based on the directives of the M.P.E.P (803.02). This has been considered but not found persuasive. Section 803.02 of the M.P.E.P. states that:

> If the members of the Markush group are sufficiently few in number or so closely related that a search and examination of the entire claim can be made without serious burden, the examiner must examine all the members of the Markush group in the claim on the merits, even though they are directed to independent and distinct inventions.

A search in the PTO pending patent databases using SEQ ID NO:74 did not result in any hits with any other SEQ ID NO in the instant application. A similar search was done using the polypeptide of SEQ ID NO:37. The data was examined down to the level of 3.1% and 32% sequence identity, respectively. The polynucleotides of SEQ ID NO:1-37 and the polynucleotide encoding SEQ ID NO:38-74 are therefore structurally distinct, thus the search for SEQ ID NO:74 and the polynucleotides encoding SEQ ID NO:37 will not be coextensive with the search for SEQ ID NO:38-76 and the polynucleotides encoding SEQ ID NO:1-36. Database size and resource allocations at the PTO are now such that examination of more than one polynucleotide encoding a protein would result in a severe burden on Office resources.

Applicant further argues that it is improper for the Patent Office to refuse to examine that which applicants regard as their invention unless the subject matter in a claim lacks unity of invention. Applicant points out that Section 803.02 of the M.P.E.P. states:

> Since the decisions in In re Weber, 580 F.2d 455, 198 USPQ 328 (CCPA 1978) and In re Haas, 580 F.2d 461, 198 USPQ 334 (CCPA 1978), it is improper for the Office to refuse to examine that which applicants regard as their invention, unless the subject matter in a claim lacks unity of invention. In re Harnish, 631 F.2d 716, 206 USPQ 300 (CCPA 1980); and Ex parte Hozumi, 3 USPQ2d 1059 (Bd. Pat. App. & Int. 1984). Broadly, unity of invention exists where compounds included within a Markush group (1) share a common utility, and (2) share a substantial structural feature disclosed as being essential to that utility.

This has been considered but not found to be a persuasive. The M.P.E.P. defines unity of invention as a sharing of a common utility and a sharing of a substantial structural feature disclosed as being essential to that utility. For the reasons set forth in the rejection under 35 U.S.C. 101 below, and the rejection of July 3, 2000 in application number 08/870,870, the polynucleotides encoding SEQ ID NO:37, 2, 6, 7, 11, 18, 19, 22, 25, 28 and 33 or the polynucleotides of SEQ ID NO:74, 39, 43, 44, 48, 55, 56, 59, 62, 65, and 70 do not share a

common utility as neither a specific, substantial, credible utility nor a well-established utility has been set forth for either group of polynucleotides, nor is a structural feature disclosed which was common to both groups of polynucleotides.

Applicant further argues that an election of species rather than a restriction requirement should have been proposed for the separation of the various SEQ ID NO recited in claims 24, 27 and 32. Applicant sets forth the an example from the M.P.E.P.(803.02):

> As an example, in the case of an application with a Markush-type claim drawn to the compound C-R, wherein R is a radical selected from the group consisting of A, B, C, D, and E, the examiner may require a provisional election of a single species, CA, CB, CC, CD, or CE. The Markush-type claim would then be examined fully with respect to the elected species and any species considered to be clearly unpatentable over the elected species. If on examination the elected species is found to be anticipated or rendered obvious by prior art, the Markush-type claim and claims to the elected species shall be rejected, and claims to the non-elected species would be held withdrawn from further consideration. As in the prevailing practice, a second action on the rejected claims would be made final.

This has been carefully considered but not found persuasive. The instant SEQ ID NO: have no common structural element that could be assigned to part "C" of the above example. The instant Markush groups do not contain a species "C-R", wherein R is variant. Thus, the example has no bearing on the instant restriction requirement.

For these reasons the restriction requirement is deemed to be proper and is adhered to. The requirement is therefore made FINAL.

2. Claims 1-22 have been canceled. Claims 23-42 have been added. Claims 23, 24, 34-38 and 40, drawn to non-elected inventions, are withdrawn from consideration. Claims 25-33, 39, 41 and 42 are examined on the merits.

Claim Objections

3. Claims 25-32 are objected to because of the following informalities:

(A) Claims 25-31 are dependent upon non-elected claims,

(B) Claims 27, 31 and 32 recite non-elected SEQ ID NO.

Appropriate correction is required.

Claim Rejections - 35 USC § 101 and 35 USC § 112

4. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

5. Claims 25-33, 39, 41 and 42 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific, substantial, credible asserted utility or a well-established utility.

The instant claims are drawn to the polynucleotide of SEQ ID NO:74 and the polynucleotides encoding SEQ ID NO:37. The instant application has provided a description of isolated polynucleotides encoding proteins and the proteins encoded thereby. The specification has collectively termed these proteins "NHRP". The instant application does not disclose the biological role for the NHRP protein of SEQ ID NO:37 or its significance. The instant specification asserts that it provides compositions which are useful in the diagnosis, prevention and treatment of diseases associated with cell proliferation, particularly immune responses and cancers (page 6, lines 1-4). The specification asserts that in cancers or immune disorders where NHRP is an "activator, transcription factor, enhancer, is being expressed, and is promoting cell proliferation; it is desirable to decrease the expression of NHRP" (page 44, lines 11-14). In cases where NHRP is an inhibitor or suppressor and not controlling cell proliferation it is desirable to provide the NHRP protein or increase the expression of NHRP (page 44, lines 14-16). The specification asserts that administration of NHRP of fragments thereof can be used to treat cancers such as "adenocarcinoma, leukemia, lymphoma, melanoma, myeloma, sarcoma, and teratocarcinoma", which include but are not limited to cancers of the "adrenal gland, bladder, bone, bone marrow, brain, breast, cervix, gall bladder, ganglia, gastrointestinal tract, heart, kidney, liver, lung, muscle, ovary, pancreas, parathyroid, penis, prostate, salivary glands, skin,

spleen, testis, thymus, thyroid, and uterus" (page 44, lines 17-23). The specification asserts that antagonist which decrease the activity of NHRP may be administered to prevent or treat "AIDS, Addison's disease, adult respiratory distress syndrome, allergies, anemia, asthma, atherosclerosis, bronchitis, cholecystitis, Crohn's disease, ulcerative colitis, atopic dermatitis, dermatomyositis, diabetes mellitus, emphysema, atrophic gastritis, glomerulonephritis, gout, Graves disease, hyper eosinophilia, irritable bowel syndrome, lupus erythematosus, multiple sclerosis, myasthenia gravis, myocardial or pericardial inflammation, osteoarthritis, osteoporosis, pancreatitis, polymyositis, rheumatoid arthritis, scleroderma, Sjogren's syndrome, and autoimmune thyroiditis; complications of cancer, hemodialysis, extracorporeal circulation, viral, bacterial, fungal, parasitic, protozoal, and helminthic infections and trauma". The specification also asserts that administration of an antagonist of NHRP could treat or prevent cancers such as "adenocarcinoma, leukemia, lymphoma, melanoma, myeloma, sarcoma, and teratocarcinoma and particularly cancers of the adrenal gland, bladder, bone, bone marrow, brain, breast, cervix, gall bladder, ganglia, gastrointestinal tract, heart, kidney, liver, lung, muscle, ovary, pancreas, parathyroid, penis, prostate, salivary glands, skin, spleen, testis, thymus, thyroid, and uterus" (page 44 line 29 to page 45 line 22).

These utilities are not considered to be specific and substantial because the specification fails to disclose any particular function or biological significance for the NHRP proteins, or the specific NHRP protein of SEQ ID NO:37. The disclosed protein of SEQ ID NO:37 is purported to have a potential function based upon the association of the polynucleotide with cDNA libraries which are immortalized or cancerous and show inflammatory or immune responses (page 32, lines 24-30). After further research, a specific and substantial credible utility might be found for the claimed isolated polynucleotides. This further characterization, however, is part of the act of invention and until it has been undertaken the claimed invention is incomplete.

The specification states that the polynucleotides encoding the NHRP of the instant invention may be used for the diagnosis of conditions or diseases which are associated with

expression of NHRP such as adenocarcinoma, leukemia, lymphoma, melanoma, myeloma, sarcoma, and teratocarcinoma and cancers of the adrenal gland, bladder, bone, bone marrow, brain, breast, cervix, gall bladder, ganglia, gastrointestinal tract, heart, kidney, liver, lung, muscle, ovary, pancreas, parathyroid, penis, prostate, salivary glands, skin, spleen, testis, thymus, thyroid, and uterus; and immune disorders such as AIDS, Addison's disease, adult respiratory distress syndrome, allergies, anemia, asthma, atherosclerosis, bronchitis, cholecystitis, Crohn's disease, ulcerative colitis, atopic dermatitis, dermatomyositis, diabetes mellitus, emphysema, atrophic gastritis, glomerulonephritis, gout, Graves disease, hyper eosinophilia, irritable bowel syndrome, lupus erythematosus, multiple sclerosis, myasthenia gravis, myocardial or pericardial inflammation, osteoarthritis, osteoporosis, pancreatitis, polymyositis, rheumatoid arthritis, scleroderma, Sjogren's syndrome, and thyroiditis (page 56, lines 2-15).

In order for a polynucleotide to be useful for diagnosis of a disease, as asserted, there must be a well-established or disclosed correlation or relationship between the claimed polynucleotide and a disease or disorder. The presence of a polynucleotide in inflamed tissues or in tissues derived from cancer cells is not sufficient for establishing a utility for the diagnosis of disease absent information regarding a correlative or causal relationship between the expression of the claimed cDNA and the disease. If a molecule is to be used as a surrogate for a disease state, some disease state must be identified in some way with the molecule. There must be some expression pattern that would allow the claimed polynucleotide to be used in a diagnostic manner. Many proteins are expressed in normal tissues and diseased tissues. Therefore, one needs to know that the claimed polynucleotide is either present only in diseased tissue to the exclusion of normal tissue, or is expressed in higher levels in diseased tissue compared to normal tissue. Evidence of a differential expression might serve as a basis for use of the claimed polynucleotide as a diagnostic for a disease. However, in the absence of any disclosed relationship between the claimed polynucleotide or the protein that is encoded thereby and any disease or disorder, and the lack of any correlation between the claimed polynucleotide or the encoded protein with any

known disease or disorder, any information obtained in an effort to establish a differential expression pattern would constitute further research on the polynucleotide itself. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner*, 148 USPQ at 696.

The instant claims are drawn to a protein of as yet undetermined function or biological significance. There is no evidence of record or any line of reasoning that would support a conclusion that SEQ ID NO:37 or the polynucleotides encoding SEQ ID NO:37 of the instant application was, as of the filing date, useful for diagnosis, prevention and treatment of cell proliferation or immune response disorders or cancers, as stated above. Until some actual and specific significance can be attributed to the protein identified in the specification as SEQ ID NO:37, or the gene encoding it, one of ordinary skill in the art would be required to perform additional experimentation in order to determine how to use the claimed invention. Thus, there was no immediately apparent or "real world" utility as of the filing date.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 25-33, 39, 41 and 42 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific, substantial, credible asserted utility or a well-established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

In the event that applicants might be able to overcome the 35 USC 101 rejection above, the specification would still be enabling only for claims limited to polynucleotides that encode SEQ ID NO:37; polynucleotides comprising SEQ ID NO:74, the complete complement of SEQ ID NO:74, an isolated polynucleotide consisting of a fragment of the complement of SEQ ID

NO:74, wherein the fragment is at least 60 contiguous residues of SEQ ID NO:74; and an array comprising a polynucleotide complementary to SEQ ID NO:74, wherein said polynucleotide is completely complementary to SEQ ID NO:74; because the specification does not reasonably provide enablement for polynucleotides that encode a fragment of SEQ ID NO:37, polynucleotides encoding polypeptides having at least 90% identity to SEQ ID NO:37, polynucleotides comprising naturally occurring polynucleotides having at least 90% sequence identity to SEQ ID NO:74 and complement and RNA equivalent thereof, an isolated polynucleotide comprising at least 60 contiguous nucleotides of SEQ ID NO:74 or the complements thereof, polynucleotides at least 90% identical to SEQ ID NO:74 or the complements thereof; micorarrays or arrays comprising SEQ ID NO:74 or microarrays or arrays comprising polynucleotides at least 90% identical to SEQ ID NO:74; arrays comprising oligonucleotides which are not completely complementary to SEQ ID NO:74 or RNA equivalents to any of the claimed polynucleotides. The specification does not enable any person skilled in the art to which it pertains or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

(A) As drawn to polynucleotides encoding a polypeptide comprising an amino acid sequence at least 90% identical to SEQ ID NO:37 and polynucleotides comprising a polynucleotide sequence at least 90% identical to SEQ ID NO:74 and the partial complements thereof, and partial complements of SEQ ID NO:74.

Claims 25, 28-30, 32, 33, 39, 41 and 42 encompass polynucleotides comprising non-disclosed nucleic acid sequences, that is polynucleotide variants of SEQ ID NO:74, polynucleotides which encode variant polypeptide of SEQ ID NO:37, and complementary polynucleotides which have partial complementarity to SEQ ID NO:74, and polynucleotides having 90% sequence identity to SEQ ID NO:74. The specification on page 12 states that "complementary" is "the natural binding of polynucleotides under permissive salt and temperature conditions by base pairing...Complementarity between two single stranded molecules may be

"partial" in which only some of the nucleic acids bind, or may be complete". Thus claims drawn to complementary sequences may contain nucleic acid residues which are not in the 3' strand of SEQ ID NO:74, or in the 3' strand of the polynucleotide encoding SEQ ID NO:37. The specification does not teach polynucleotides encoding a naturally occurring polypeptide having 90% identity to SEQ ID NO:37 or naturally occurring polynucleotides having 90% identity to SEQ ID NO:74. The specification states that alleles result from at least one mutation in the nucleic acid sequence and may result in mRNAs or polypeptides whose structure or function may or may not be defined (page 10, lines 1-4). The specification states that altered nucleic acid sequences encoding NHRP include those with deletions, substitutions or insertions of different nucleotides that result in a polynucleotide that encodes the same functionally equivalent NHRP (page 10, lines 8-10). However, the specification also states that variants of NHRP include amino acid sequences having non-conservative changes in the amino acid sequence (page 17, lines 11-12).

The claims are broadly drawn to variant polynucleotides and polynucleotides encoding variant polypeptides. The specification neither limits nor defines naturally occurring polynucleotide having 90% identity to SEQ ID NO:74 or naturally occurring amino acid sequences having 90% identity to SEQ ID NO:37. The specification neither limits nor defines fragments of the amino acid sequence of SEQ ID NO:37 for the reasons set forth in the rejection under 112, second paragraph, below. Further, the variants as defined in the specification include but are not limited to allelic sequences, altered NHRP and variants of NHRP. However, since any definition recited in the specification is not limiting if absent from the claims, it is assumed for examination purposes that polynucleotides encoding amino acid sequences having at least 90% sequence identity to SEQ ID NO:37 and polynucleotides having 90% sequence identity to SEQ ID NO:74 include polynucleotides with substitutions, insertions and deletions of nucleic acid residues that will result in altered polypeptides. When given the broadest reasonable interpretation, the claims are clearly intended to encompass a large species of polynucleotides that

encode numerous proteins having neither structural nor functional identity with polynucleotides encoding SEQ ID NO:37 and no guidance has been given as to how to use these species. The specification has not shown that polynucleotides encoding polypeptides comprising variants of SEQ ID NO:37 or polynucleotide variants of SEQ ID NO:74 are capable of functioning as polynucleotides encoding SEQ ID NO:37. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with the claims since the specification gives no guidance on or exemplification of how to make/use the polynucleotides that encode the broadly claimed polypeptides. The relationship between amino acid sequence and protein function is probably one of the most unpredictable areas of biotechnology. For example, as disclosed by Burgess et al (Journal of Cell Biology, 1990, Vol. 111, pp.2129-2138) replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein (page 2132 column 1 to page 2133 column 2). In the case of TGF alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the altered TGF alpha. (Lazar et al, Molecular and Cellular Biology, 1988, Vol. 8, pp.1247-1252, page 1250 bridging paragraph). These references demonstrate that even a single amino acid substitution or what appears to be a minor modification will often dramatically affect the biological activity of a protein. Clearly, it could not be predicted that a variant polynucleotide, or polynucleotide encoding a variant protein would have equivalent functional characteristic of the polynucleotide which encodes SEQ ID NO:37. Further, one of skill in the art would not be able to screen variant polypeptides based on functional characteristic because the specification has not disclosed any regulatory, structural of biochemical characteristic of SEQ ID NO:37. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth, and it cannot be predicted from the disclosure how to make/use variant polynucleotides, or polynucleotides encoding variant proteins.

Claim 33 is drawn to an isolated polypeptide which comprises 60 contiguous nucleotides of SEQ ID NO:74, the complementary sequences thereof, or a naturally occurring polynucleotide having 90% sequence identity to SEQ ID NO:74 or the complementary sequences thereof. It is noted that claim 33 encompasses both sense and anti-sense strands of SEQ ID NO:74 and the naturally occuring variant of SEQ ID NO:74, however the specification does not teach how to use a probe comprising a sense strand of SEQ ID NO:74 or a sense strand of a naturally occurring variant of SEQ ID NO:74. Aforesaid probes would hybridize to genomic DNA, and there are no teachings in the specification or any art of record to support the notion that binding of a probe to genomic DNA would be diagnostic for the diseases and conditions recited on page 56, lines 2-15, as the recited disorders are asserted to be associated with aberrant NHRP expression in contrast to the presence of the gene in the genome. Thus, it can be concluded that the specification does not teach a use for a polynucleotide probe comprising at least 60 contiguous nucleotide residues of SEQ ID NO:74, or a naturally occurring variant of SEQ ID NO:74. Further, claim 33 is draw in part to polynucleotides comprising a polynucleotide complementary to SEQ ID NO:74 or the variants of SEQ ID NO:74. The specification indicates that complementarity can include partial complementarity and that the natural binding of the two polynucleotide strands is influenced by salt and temperature conditions. However, the specification has not taught a specific use for the partial complementary sequences as presumably they would hybridize to non-disclosed nucleic acid sequences, and the specification fails to provide an enabling disclosure for how one would use such polynucleotides.

Furthermore, claim 33 is drawn to isolated polypeptides which comprise, rather than consist of, 60 contiguous nucleotides of SEQ ID NO:74 or a variant of SEQ ID NO:74, or the complements of either of the aforesaid polynucleotides. Given the broadest reasonable interpretation, the claim reads on a large genus of polynucleotides in excess of 60 nucleotides and the specification has not a use for the broadly claimed polynucleotides. The specification has not taught that a polynucleotide sequence comprising 60 contiguous nucleotides of SEQ ID NO:74 in

addition to non-disclosed nucleotides would serve as a diagnostic indicator for the same disease states as SEQ ID NO:74. The specification has not taught that transferring 60 contiguous nucleotide of SEQ ID NO:74 into a longer polynucleotide sequence would result in polynucleotide encoding a polypeptide having the same functional characteristic of SEQ ID NO:37. It is well known in the art that proteins are folded three-dimensional structures, the function and stability of which are directly related to a specific conformation (Mathews and Van Holde, Biochemistry (text), 1996, pp. 165-171). In any given protein amino acids distant from one another in the primary sequence may be closely located in the folded three-dimensional structure. (Mathews and Van Holde, figure 6.1). The specific conformation of a protein results from non-covalent interactions between amino acids, beyond what is dictated by the primary amino acid sequence. A different amino acid sequence surrounding a fragment of the NHRP of SEQ ID NO:37 protein can potentially radically alter the three dimensional structural environment in which the given fragment is located (Matthews in Perspectives in Biochemistry, 1989, Ed. H. Neurath, pp. 6-9, page 6, second column, first paragraph) and the consequences of the altered sequence environment cannot be predicted. Additionally, it is recognized in the art that protein function is context dependent, and cellular aspects must be considered with respect to protein function in addition to molecular aspects (Bork, Genome Research, 2000, vol. 10, pp. 398-400, p. 398, column 2, first paragraph). Furthermore, it would be expected that a substantial number of the complementary polynucleotides encompassed by the claims would not share functional properties with the polynucleotides of SEQ ID NO:74 or encode proteins that share functional properties of SEQ ID NO:37. The function of the claimed polynucleotides cannot be predicted, and has not been taught by the specification. Thus, with the exception of a polynucleotide sequence consisting of 60 contiguous amino acid sequence of the complete complement of SEQ ID NO:74, one of skill in the art would be forced into undue experimentation in order to use the broadly claimed polynucleotides..

(B) An array comprising: SEQ ID NO:74, an array comprising a polynucleotide having at least 90% sequence identity to SEQ ID NO:74, an array comprising the partial or complete complement of a polynucleotide having at least 90% sequence identity to SEQ ID NO:74

Claims 39, 41 and 42 are drawn to arrays comprising fragments of the polynucleotides of claim 32 and 33. It is noted that the polynucleotides encompass both sense and anti-sense strands of SEQ ID NO:74 and variants of SEQ ID NO:74, and for the reasons states above, the specification is not enabling for probes consisting of the sense strand of SEQ ID NO:74 or a variant of SEQ ID NO:74 as the probe would hybridize to genomic DNA. Further, the specification is not enabling for probes comprising fragments of the anti-sense strand of the variant of SEQ ID NO:74 as the specification has not taught how to use all the possible variants of SEQ ID NO:74 as stated in the rejection above, regarding naturally occurring polynucleotides having at least 90% sequence identity to SEQ ID NO:74. For these reasons, one of skill in the art would not know how to use the broadly claimed arrays for the detection of the diseases stated on page 56, lines 2-15.

(C) As drawn to polynucleotides encoding fragments of SEQ ID NO:37

Claim 25 is drawn in part to polynucleotides encoding biologically active fragments or immunologically active fragments of SEQ ID NO:37.. For the reasons stated in the rejection under 112, second paragraph below, the term "biologically active" is not limiting and the specification has not provided an enabling disclosure for how to use all possible fragments of SEQ ID NO:37. The specification has not taught a specific domain of SEQ ID NO:37 that was associated with a specific enzymatic, receptor or binding activity, wherein said domain would retain its function apart from the sequence context of SEQ ID NO:37. The specification has not taught any regulatory, structural or biochemical functions of SEQ ID NO:37 and therefore has not enabled the scope of the claims drawn to biologically active fragments of SEQ ID NO:37. One of skill in the art would not know how to screen fragments of SEQ ID NO:37 for the putative biologically active fragments without some guidance as to the biological activities of SEQ ID

NO:37. Claim 25 is also drawn in part to immunologically active fragments of SEQ ID NO:37. For the reasons stated in the rejection under 112, second paragraph below, the term "immunologically active" is not limiting. The specification states that antibodies which specifically bind NHRP may be used for the diagnosis and conditions or diseases characterized by expression of NHRP, or in assays to monitor patients being treated with NHRP, agonists, antagonists or inhibitors (page 54, lines 17-19). Further, the specification has not provided teachings for how to use any antibody generated to peptides of SEQ ID NO:37. The specification contemplates the administration of antibodies which specifically bind NHRP may be used directly as an antagonist or may be used indirectly as a targeting or delivery mechanism for bringing a pharmaceutical agent to cells or tissues which express NHRP. The specification has not taught how to make antibodies which antagonize the action of the NHRP of SEQ ID NO:37 as the specification has not taught a receptor or a ligand for NHRP. The specification has not taught if NHRP is expressed on the cell surface as an antigenic target, or if NHRP is involved in signal transduction within the cytosol, or if NHRP binds directly or indirectly to nuclear DNA. Without a specific function attributable to the NHRP of SEQ ID NO:37 one would not know if an antibody which bound to SEQ ID NO:37 was able to antagonize said function or inhibit a putative binding with a ligand or receptor. Further, with regard to the delivery of a pharmaceutical to a disease site, the specification does not teach that SEQ ID NO:37 is accessible on the cell surface. Given this lack of teaching, one of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to use the broadly claimed fragments of SEQ ID NO:37.

(D) As drawn to RNA equivalents of the claimed polynucleotides

Claim 32, part e, is drawn to RNA equivalents of polynucleotides comprising SEQ ID NO:74 and complements thereof, polynucleotides comprising naturally occurring polynucleotides at least 90% identical to SEQ ID NO:74 and complements thereof. Claims 33, 39, 41 and 42 embody in part the RNA equivalents of claim 32. The specification has not provided an enabling

disclosure for the polynucleotides, arrays and microarrays of claims 32 (b, c and d), 33, 39, 41 and 42 for the reasons set forth in the sections above. Further, the specification has failed to define the structure of function of an "RNA equivalent", thus one of skill in the art would not be able to make or use the claimed RNA equivalents encompassing the polynucleotides of claim 32, sections a, b, c or d or the claimed arrays and microarrays dependent upon the RNA equivalents of claim 32.

The specification provides insufficient guidance with regard to all of the issues above and provides no working examples which would provide guidance to one skilled in the art on how to use the broadly claimed species. For the above reasons, undue experimentation would be required to practice the claimed invention.

8. Claims 25, 28, 29, 30, 32, 33, 39, 41 and 42 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 25, 28-30 are dependent on non-elected claim 23. New claims 23, 32, 41 and 42 have added new matter not present in the specification or claims as originally filed. The added material which is not supported by the original disclosure is as follows:

(A) naturally occurring amino acid sequences at least 90% identical to an amino acid sequence selected from the group consisting of SEQ ID NO:1-37 (new claim 23), and

(B) a polynucleotide comprising a naturally occurring polynucleotide sequence at least 90% identical to a polynucleotide sequence selected from the group consisting of SEQ ID NO:38-74 (new claim 32).

The specification contemplates allelic sequences on page 10, lines 1-7, and NHRP variants having 90% sequence identity the NHRP sequence, however, this is not adequate basis for

naturally occurring amino acid sequences having at least 90% identity to SEQ ID NO:37 or naturally occurring polynucleotide sequences having 90% sequence identity to SEQ ID NO:74.

(C) an array comprising ...a polynucleotide sequence specifically hybridizable with at least 30 contiguous nucleotides of a target polynucleotide (new claim 41),

(D) an array....complementary to at least 30 contiguous nucleotides (new claim 42)

(E)a microarray wherein at least one element of the microarray is a polynucleotide of claim 33 (new claim 39).

The specification teaches a specific example of a microarray produced from SEQ ID NO:38-74, wherein the sequence specific oligonucleotides are 20 nucleotides in length. The specification does not contemplate any other length for the oligonucleotide probes in an array or microarray. The introduction of "hybridizable with at least 30 contiguous nucleotides of a target polynucleotides" in claims 41 and 42 is beyond the scope of what was contemplated in the specification as originally filed as there is no support for oligomers longer than 20 nucleotides (page 67, Example VII). The addition of claim 39 drawn to a microarray comprising a polynucleotide comprising at least 60 contiguous nucleotides of claim 32 is also beyond the scope of what was contemplated in the specification as originally filed due to the length of the oligonucleotide (at least 60 contiguous nucleotide) in the array, and due to the dependence on claim 32, drawn in part to complements of polynucleotides comprising naturally occurring sequences having at least 90'% identity to SEQ ID NO:74. The specification or originally filed claims did not contemplate arrays comprising oligonucleotides complementary to polynucleotide having 90% identity to SEQ ID NO:74.

Because of the introduction of new matter, one of skill in the art would not be reasonablely assured that applicant had possession of the claimed invention at the time of filing.

9. Claims 25, 28, 29, 30 and 32 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 25 is drawn in part to polynucleotides encoding polypeptides comprising a naturally occurring amino acid sequence at least 90% identical to SEQ ID NO:37 and (for the reasons stated below in the rejection under 35 U.S.C. 112, second paragraph), polynucleotides encoding fragments of SEQ ID NO:37. Claim 28 specifically embodies the polynucleotide of claim 25 wherein a promoter is operably linked to said polynucleotide. Claim 29 specifically embodies a cell transformed with the recombinant polynucleotide of claim 28. Claim 30 is drawn in part to methods of producing polypeptides comprising a naturally occurring amino acid sequence at least 90% identical to SEQ ID NO:37 and (for the reasons stated above in the rejection under 35 U.S.C. 112, second paragraph) fragments of SEQ ID NO:37. Claim 32 is drawn in part to a polynucleotide comprising a naturally occurring polynucleotide sequence at least 90% identical to SEQ ID NO:37, a complement(part d) and RNA equivalent (part e) thereof. Claim 32 is also drawn in part to the complementary sequence of SEQ ID NO:38-74(part c) and an RNA equivalent of said complementary sequence (part e).

The written description in this case only sets forth polynucleotides encoding SEQ ID NO:37, polynucleotides comprising SEQ ID NO:74, and equivalent degenerative codon sequences thereof and therefore the written description is not commensurate in scope with the claims drawn to polynucleotides encoding naturally occurring amino acids sequences having 90% sequence identity to SEQ ID NO:37 or polynucleotides comprising a naturally occurring polynucleotide sequences at least 90% identical to SEQ ID NO:74,

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the "written description" inquiry, whatever is now claimed. (See page 1117). The specification does not clearly allow persons of

ordinary skill in the art to recognize that [he or she] invented what is claimed. (See Vas-Cath at page 1116).

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

The claims are drawn to a genus of variant polynucleotides and neither the common attributes of the genus nor specific examples of species representative of the genus have been described. The structures of naturally occurring polynucleotides having 90% sequence identity to SEQ ID NO:74 and polynucleotides encoding polypeptide having 90% sequence identity to SEQ ID NO:37 are not defined by structure or function and cannot be anticipated from the art.

With the exception of SEQ ID NO:74, and the polynucleotides encoding SEQ ID NO:37, the skilled artisan cannot envision the detailed structure of the encompassed polynucleotides and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Lts., 18 USPQ2d 1016.

For the reasons set forth above, the specification is insufficient to support the generic claims as provided by the Interim Written Description Guidelines published in the January 5, 2001 Federal Register at Volume 66, Number 4, pages 1099-1111.

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 25-33, 39, 41 and 42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 25-31 depend on claim 23 which recites "a naturally occurring amino acid sequence at least 90% identical to an amino acid sequence...". It is unclear how the origin of the polypeptide, natural versus synthetic, can alter the properties of a polynucleotide which would encode said polypeptide. For purpose of examination, claims 25 will be read on claim 23, part b, as a polynucleotide encoding a polypeptide comprising an amino acid sequence having 90% sequence identity to SEQ ID NO:37.

Claim 32 recites "a polynucleotide comprising a naturally occurring polynucleotide sequence at least 90% identical to a polynucleotide...". It is unclear how the origin of the polynucleotide comprising a naturally occurring sequence influences the propertied of the claimed polynucleotides. Further, the metes and bounds of the claims cannot be determined as it is unclear if "naturally occurring" is meant to exclude only chemically synthesized polynucleotides, or if "naturally occurring" also excludes recombinant polynucleotides which have been replicated in a cell or mRNA which has been expressed from a vector. For purpose of examination, claim 32, part b, will be read as a polynucleotide comprising a sequence at least 90% identical to SEQ ID NO:74.

Claims 25, 28, 29 and 30 depend on non-elected claim 23 (part c) which recites, a biologically active fragment of a polypeptide having an amino acid sequence of SEQ ID NO:37 and (part d), an immunogenic fragment of a polypeptide having an amino acid sequence of SEQ ID NO:37. The specification defines "biologically active" and "immunologically active" on page 12, lines 4-8, "refers to a protein having structural, regulatory, or biochemical functions of a naturally occurring molecule. Likewise, "immunologically active" refers to the capability of the natural, recombinant or synthetic NHRP, or any oligopeptide thereof, to induce a specific immune response in appropriate animals or cells and to bind to specific antibodies." As the structural, regulatory and biochemical functions of SEQ ID NO:37 are not defined by the specification, the metes and bounds of what constitute a "biologically active" fragment of SEQ ID NO:37 cannot be construed. Further, as the "specific immune response", "appropriate animals or cells" and

"specific antibodies" are not limited by the definition given in the specification. As such, "immunologically active" can encompass any fragment of SEQ ID NO:37 as any fragment of SEQ ID NO:37 can induce an immune response in an organism which would recognize the fragment as non-self.. Likewise, inoculation of the aforesaid organism with any fragment of SEQ ID NO:37 will give rise to an antibody which will bind the fragment. Further, it is unclear how a specific immune response can be induced in a single cell, as immune responses in any mammalian organism require many types of cells and organs and cannot be duplicated by a single cell. Thus the qualification of "immunologically active" does not serve to limit the fragments of SEQ ID NO:37.

Claim 32 (part e) is vague and definition in the recitation of "an RNA equivalent" as the specification does not contain a definition for what constitutes said "equivalent". It is unclear if the claim is intended to encompass RNA species which differ from the disclosed DNA sequences by more than the substitution of U for all Ts.

Claim 41 recites "specifically hybridizable". The specification states that "Hybridization occurs with precise complementary matches or with various degrees of less complementarily""". It is unclear what degree of complementarily is encompassed by "specifically hybridizable".

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claim 32 is rejected under 35 U.S.C. 102(b) as being anticipated by the New England Biolabs Catalog, 1994, page 91.

Claim 32 is drawn in part to a polynucleotide sequence complementary to SEQ ID NO:74 and a polynucleotide sequence complementary to a polynucleotide comprising a naturally occurring polynucleotide sequence at least 90% identical to SEQ ID NO:74.

The New England Biolabs Catalog discloses random hexamers which will be complementary to SEQ ID NO:74 or to a naturally occurring sequence having at least 90% identity to SEQ ID NO:74.

Double Patenting

14. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

15. Claims 25, 28, 29, 30, 32, 33, 39, 41 and 42 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 5, 6 and 7 of copending Application No. 09/539,800. Although the conflicting claims are not identical, they are not patentably distinct from each other. Claim 25 is drawn in part to

polynucleotides encoding a fragment of SEQ ID NO:37 (for the reasons stated in the rejection under 112, second paragraph, above). Claim 28 specifically embodies the polynucleotide of claim 25 wherein a promoter is operably linked to said polynucleotide. Claim 29 specifically embodies a cell transformed with the recombinant polynucleotide of claim 28. Claim 30 is drawn in part to methods of producing a polypeptide of claim 23 comprising recombinant expression. Claim 32 is drawn in part to the complementary sequence of SEQ ID NO:74. Claim 33 embodies an isolated polynucleotide comprising at least 60 contiguous nucleotide of the polynucleotides of claim 32. Claim 39 is drawn to a micro array wherein at least one element is a polynucleotide of claim 33. Claim 41 is drawn to an array comprising a first polynucleotide or oligonucleotide sequence specifically hybridizable with at least 30 contiguous nucleotide of the polynucleotides of claim 32. Claim 42 is drawn to the array of claim 41 wherein said first polynucleotide or oligonucleotide sequence is completely complementary to at least 30 contiguous nucleotides of the polynucleotides of claim 32. The instant specification states that "complementary" includes "partial" complementarity (page 12, lines 12-13). Nucleotides 17-239 of SEQ ID NO:1385 of the '800 application are identical to nucleotides 1011-1233 of the instant SEQ ID NO:74. Claim 1, part c, of the '800 application is drawn in part to a complement of SEQ ID NO: 1385 and said complement would be partially complementary to the instant SEQ ID NO:74. Thus claim 1, part c is drawn to a species of the instant genus comprising a polynucleotide which is complementary to the polynucleotides of claim 32, part c. Further the complement of the nucleotides 17-239 of SEQ ID NO:1385 are completely complementary to more than 60 contiguous nucleotides of SEQ ID NO:74, thus fulfilling the specific embodiments of instant claim 33. Claim 1, part b, of the '800 application is drawn to a fragment of SEQ ID NO:1385; SEQ ID NO:1385 encodes amino acid residues 257-329 of the instant SEQ ID NO:37. Thus claim 1, part b, as drawn to SEQ ID NO:1385 is a species of the instant claim 25, drawn in part to polynucleotides encoding a fragment of SEQ ID NO:37. Claims 2, 5, 6 and 7 of the '800 application drawn to compositions and expression vectors comprising the polynucleotides of claim 1, host cells comprising the

expression vectors of claim 5 and a method of producing a polypeptide comprising the recombinant expression of the host cell of claim 6 are thus species of the instant claims 28, 29 and 30. Further, claims 1, 2 and 4 of the '800 application anticipate claims 32 and 33 of the instant application, as the claims are drawn to complementary sequences. The instant application defines "micro array" on page 14, lines 21-22, as oligonucleotides synthesized on a substrate. Claim 3 of the '800 application, drawn to a substrate comprising at least one polynucleotide of claim 1 thus anticipates the instant claims 39, 41 and 42.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

16. All claims are rejected.

Conclusion

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Canella, Ph.D.
Patent Examiner, Group 1642
September 9, 2002